

Remarks

Reconsideration of this Application is respectfully requested.

I. Status of the Claims

Upon entry of the foregoing amendment, claims 77-80 and 82-98 are pending in the application, with claims 77 and 94 being the independent claims. Claims 77 and 94 are sought to be amended. Support for the amendments to claims 77 and 94 can be found, *inter alia*, in the as-filed specification at page 9, line 12, through page 10, line 3. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

II. Rejection of Claims 77-80 and 82-98 Under 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 77-80 and 82-98 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 6,187,765 B1 to Harris *et al.* (hereinafter "Harris"). (Office Action, page 3, lines 17-18). Applicants respectfully traverse the rejection.

The Examiner states that Harris "does not teach a method of preparing a sterile suspension of steroid where the steps are in the same order as claimed." (Office Action, page 5, lines 3-4). The Examiner also acknowledges that Harris "teaches extra steps, such as isolating and drying the steroid." (Office Action, page 5, lines 11-12). However,

the Examiner alleges that "the extra step of isolating the product is not essential because it does not materially affect the end product." (Office Action, page 5, lines 13-15). Applicants respectfully disagree.

Amended claim 77 is directed to a method for preparing a sterile pharmaceutical composition of a steroid comprising: (i) dissolving a non-sterile steroid in a solvent to yield a solution of the steroid, (ii) filtering the solution of (i) to yield a sterile solution, (iii) combining the sterile solution of (ii) with sterile water to form a suspension, (iv) optionally removing all or part of the solvent from the suspension of (iii), (v) treating the sterile suspension of (iii) or (iv) to obtain a suspension with a particle size distribution having a mass median diameter less than 10 μm , (vi) under sterile conditions combining the suspension of (v) with a pharmaceutically acceptable carrier to yield a sterile pharmaceutical composition comprising a suspension of the steroid having a mass median diameter less than 10 μm , and (vii) storing the sterile pharmaceutical composition of (vi) in sterile containers.

Amended claim 94 is directed to a method for preparing a sterile suspension of budesonide, comprising: (i) dissolving non-sterile budesonide in a solvent to yield a budesonide solution, (ii) filtering the solution of (i) to yield a sterile solution, (iii) combining the sterile solution of (ii) with sterile water to form a suspension of budesonide, (iv) optionally removing all or part of the solvent from the suspension of (iii), (v) treating the sterile suspension of (iii) or (iv) to obtain a suspension with a particle size distribution having a mass median diameter less than 10 μm , (vi) under sterile conditions combining the suspension of (v) with a pharmaceutically acceptable carrier to yield a sterile pharmaceutical composition comprising the suspension of

budesonide having a mass median diameter less than 10 μm , and (vii) storing the sterile pharmaceutical composition of (vi) in sterile containers.

As can be seen in amended claims 77 and 94, the solution, suspension or composition referred to in each step is clearly that obtained in a preceding step of the method. Any drying step is precluded by reference to *the* solution of a previous step, *the* suspension of a previous step, or *the* composition of a previous step as appropriate. There is no drying step between forming the sterile suspension (iii) and storing the pharmaceutical composition of (vi). If the suspension was at any point dried and resuspended, it would inherently *no longer be the suspension of the appropriate preceding step*. Thus, the input of each step is clearly defined as the output from the appropriate preceding step. Therefore, Applicants method cannot comprise an intermediate drying step as this is specifically excluded by the claim language.

Example 1 of Harris produces sterile mometasone furoate monohydrate per se by a process that finishes with a drying step, to produce a dry product (step 10 of example 1)(col. 6, lines 25-62). The dry product of Harris is then used to formulate various pharmaceutical compositions, each having different concentrations of active and excipients (see examples 2, 3, 5 and 6 at col. 6, line 65, through col. 7, line 67 and at col. 8, lines 35-67). Therefore, it would be clear to a person of skill in the art that it is essential to produce a sterile *dry* product as this is subsequently available for use in any number of sterile mometasone furoate monohydrate compositions.

Furthermore, Harris discloses that "[i]t is preferred to produce the mometasone furoate monohydrate under sterile conditions, conduct the drug micronization in a sterile environment, and perform a sterile packaging operation" (col. 5, lines 52-55). This, in

combination with examples 1, 2, 3, 5, and 6, would provide one of ordinary skill in the art with a reason to view the processes of Harris as separate and distinct parts of a two stage method.

Thus, the essential first stage of the method of Harris is to produce *dry* sterile mometasone furoate monohydrate. Conversely, the present invention provides a single stage method for preparing a sterile pharmaceutical composition of a steroid. Similarly, in *In re Freed*, 425 F.2d 785 (CCPA 1970) the claimed invention was a single-step process for producing calcium pantothenate whereas the prior art disclosed a two-stage reaction. The court held that the single-step process was not obvious over the two-step process disclosed in the prior art. The court explained that

it seems more logical and reasonable to infer that one teaching a chemical reaction process would set out the least number of reactions thought necessary to accomplish the desired objective. Thus, one skilled in the art who reads the teaching would have to presume that if the reactants were not combined in the manner shown, some adverse side reaction or no reaction at all would occur.

Id. at 788. Thus, one of ordinary skill in the art reading Harris would view a two stage method as essential and therefore, would not have a reason to use a single stage method.

Additionally, one of ordinary skill in the art would not have a reason to combine the processes of examples 1 and 2 of Harris and then, to omit the drying step of example 1. The suspension of example 1 in step 8 of Harris (col. 6, lines 53-54) comprises sterile mometasone furoate monohydrate in suspension with water and acetone. Example 2 of Harris begins by preparing a sterile excipient solution of polysorbate 80, citric acid monohydrate, sodium citrate dehydrate, and sodium chloride, to which a precise number of grams of dry mometasone furoate monohydrate are added (col. 7, lines 1-14). Thus, if the mometasone furoate monohydrate were still in suspension there would be a number

of problems including (i) the presence of acetone in the suspension, whereas this would previously have all been removed by drying and (ii) the mometasone furoate monohydrate would be in a dilute suspension comprising a large amount of water, making it difficult to calculate the precise amount of mometasone furoate monohydrate present or indeed to remove a precise amount of mometasone furoate monohydrate from the suspension. This dilute suspension could not simply be added to the excipients prepared in steps 1 and 2 of example 2 without a significant number of calculations and alterations to the process of example 2. Thus, to convert the two stage method of Harris into the single stage method of present invention would require the skilled person to make a significant number of complex changes to the processes of example 1 *and* example 2.

The skilled person reading Harris would understand that the two stage method is essential and moreover, even if they were seeking a simpler method it would not be obvious to make significant amendments to *both* parts of the Harris method in order to combine the separate processes. It would be far easier to follow the Harris method exactly as set out, producing dry sterile mometasone furoate monohydrate and mixing this with excipients as desired.

In summary, the method of the present invention does not merely amount to a reversal of the steps of the method disclosed in Harris. Rather, the present invention reorders *some* of the steps of Harris, which allows the remaining steps to be omitted and results in a single stage process that is not obvious from the disclosure of Harris.

Therefore, Harris does not provide a reason to make Applicants' claimed invention. Accordingly, Applicants respectfully request that the rejection of claims 77-

80 and 82-98 under 35 U.S.C. § 103(a) as being unpatentable over Harris be withdrawn.

III. Examiner's Response to Arguments

The Examiner alleges that Applicants argument that the claimed one-step process is not obvious over the two-step process taught by Harris is not persuasive because "it is respectfully submitted that the isolation of the steroid is a design choice and not an essential step because it does not materially affect the end product." (Office Action, page 8, lines 14-16). Applicants respectfully disagree.

The Examiner also alleges that Applicants argument that Harris does not provide a reason why one would treat a suspension of (iii) or (iv) to reduce its particle size is unpersuasive because "the addition of the pharmaceutically [acceptable] carrier before or after reducing the particle size is not considered to be a patentable modification and the isolation step is not viewed as an essential step." (Office Action, page 9, lines 4-6). Applicants respectfully disagree.

As discussed above, a person of skill in the art reading Harris would believe that it is essential to produce a sterile *dry* product as this is subsequently available for use in any number of sterile mometasone furoate monohydrate compositions. Furthermore, if one of ordinary skill in the art were to convert the two stage method of Harris into the single stage method of present invention, it would require the skilled person to make a significant number of complex changes to the processes of example 1 *and* example 2.

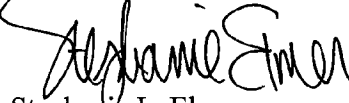
Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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